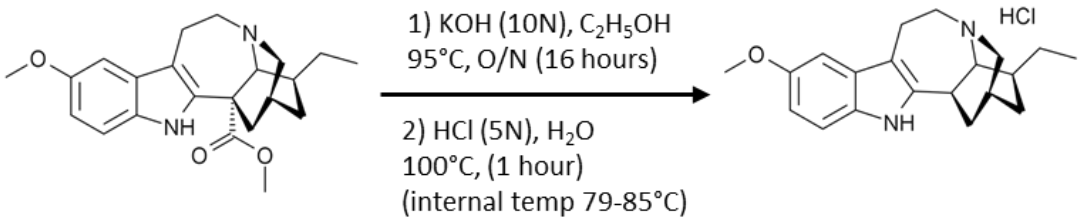
Synthesis of Ibogaine Hydrochloride



Hydrolysis:

- The slurry of pure voacangine (25 g, 67.847 mmol) in ethanol (203 mL) was prepared in 1 L RB flask, equipped with magnetic stirrer.
- To above slurry freshly prepared aqueous KOH solution (10 N, 40.7 mL) was added through dropping funnel over the period of ~5-6 minutes at room temperature.
- Dropping funnel was replaced with water condenser and the resulting slurry was heated at 95°C, which formed a transparent solution in 30-35 minutes, heating continued for 16 hours (overnight).
- TLC (R_f = 0.8 in 5% methanol in DCM) showed complete conversion of starting material.
- Hot solution was quickly filtered through Büchner funnel leaving behind some insoluble material. Flask was rinsed with ethanol (30 mL) and filtered.
- Combined filtrate was evaporated in RB flask (1 L) to complete dryness. The residue was slurred homogeneously in H_2O (100 mL) by vigorous stirring
- The slurry was evaporated on rota evaporator (at 50 ^oC) connected to high vacuum pump to remove all residual ethanol.
- The process was repeated with another 100 mL of H_2O and again evaporated to dryness on rota evaporator (at 50 ^oC) connected to high vacuum pump.

Caution: Small amount of residual ethanol will make ethyl ester with K-salt, which is difficult to remove from final compound.

Decarboxylation

- Above K-salt was dissolved in H_2O (269 mL) at 100°C in a 1 L RB flask, equipped with magnetic stirrer and dropping funnel leading to bubbler tube.
- The HCl solution (5N, 115.3 mL) was added very slowly through dropping funnel to above vigorously stirred hot solution (100 ^oC) over a period of 45 minutes.
- First 40 mL of HCl addition was moderate (4mL/min for 10 min) then there was a lot of effervescence over the surface of reaction as well as a lot of gas bubbles through the bubbler tube so the next 50 mL of HCl addition was slowed down (2mL/min for 25 min) and a final portion of 25 mL of HCl was again moderate (2.5 mL/min for 10 min).
- Dropping funnel was replaced with reflux condenser connected to bubbler tube.
- Heating at 100 ^oC was continued for one hour. Internal temperature at this stage was 79-85 ^oC. No more gas evolution through bubbler tube was observed after one hour. The heating was stopped.
- The slurry was allowed to cool to room temperature for around 15-20 min and then left in a cold room (4 ^oC) for 4 hours.
- The cold slurry was filtered through Buchner funnel and rinsed with H_2O (20 mL).
- The resulting light-yellow solid was air dried to constant weight.
- Crude 21.78 g, 92.5% recovery.

Purification

- 10% aqueous EtOH (274 mL i.e., 12.58 mL/g) was gradually added to the crude ibogaine hydrochloride and refluxed until all solid was dissolved
- The hot solution was filtered quickly Buchner funnel (no washings). The filtrate was allowed to cool to room temperature then left in a cold room (4 ^oC) overnight.
- The cold slurry was filtered and washed with 5% aqueous ethanol (25 mL).
- Shiny pearl solid was air dried to constant weight to get 1st crop (15.12 g, 64%).
- Above filtrate was completely evaporated to get a constant weight (6.35 g)

- Above solid (6.35 g) was dissolved in 10% aqueous ethanol (79 mL, which was added gradually to refluxing solution until all solid dissolved).
- The hot solution was allowed to cool to room temperature then left in the cold room (4 ^{o}C) for 4 hours.
- The cold slurry was filtered and washed with 5% aqueous ethanol solution (2 x 20 mL). The white solid was air dried to constant weight to get 2nd crop (3.60 g, 15.3%).
- 1st crop and 2nd crop were mixed homogeneously to obtain a single batch (RPI-014-144-PP) 18.72 g, 79.5%
- NMR is clean, HPLC 99.91% with single major impurity is 0.06%. Mass consistent with structure (M+H = 311.0), melting point: 289 decomposed.

2 other 25 g batches were also done following the same procedure.

The yield is 18.78 g, 79.8% (RPI-014-148-PP) and 18.71 g, 79.5% (RPI-014-149-PP) with the same purity profile.

All analytical data are attached with the procedure.